

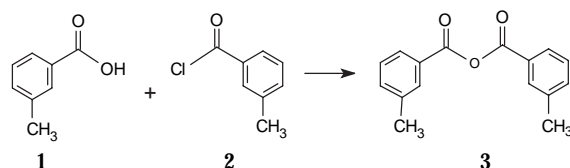
A Modified Synthesis of the Insect Repellent DEET

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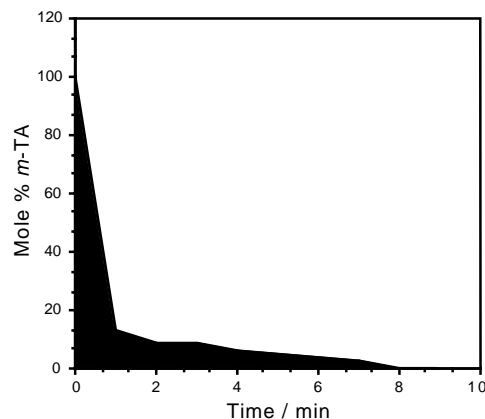
A popular organic lab is the preparation of diethyltoluamide (DEET), the active ingredient in Off and Deep Woods insect repellents. Lab procedures uniformly prepare the *m*-toluoyl chloride intermediate by heating *m*-toluic acid (1) with thionyl chloride (SOCl₂) for times ranging from 15 to 45 minutes (1). Subsequent reaction of the *m*-toluoyl chloride (2) with diethylamine and basic workup gives DEET. However, using a similar procedure, our students consistently produced DEET as a dark brown oil which was contaminated with a by-product as seen by infrared (IR) spectroscopy, and unfortunately, they never had enough time to vacuum-distill the crude DEET.¹ The students' parting comment that they'd "rather be bitten by mosquitoes" than use their product prompted a reexamination of the DEET synthesis.

The infrared (IR) spectrum of the crude DEET showed two strong bands at 1763 and 1720 cm⁻¹, which were unrelated to DEET's structure. We suspected that the two IR bands represented the symmetrical and asymmetrical C=O stretch of the conjugated anhydride (3).



GC/MS analysis of the crude DEET confirmed the presence of the impurity at 12.5 minutes.² The parent ion, a *m/e* peak of 254, corresponded to the molecular weight of the expected anhydride. Also strong peaks at *m/e* = 119 and 91 supported the anhydride H₃C-C₆H₄-C=O and C₆H₄-CH₃ fragments. A final independent synthesis of the *m*-toluic anhydride showed identical retention time and mass spectrum as the DEET by-product (2).

We attributed the dark color of our DEET product to the initial heating needed to form the *m*-toluoyl chloride. We wondered if the absence of heating might eliminate this dark coloration and also reduce the formation of the anhydride. The reaction was repeated with a few modifications. To an *m*-toluic acid/ether suspension was added a catalytic amount of pyridine followed by SOCl₂. The reaction mixture was stirred at room temperature with no heating. Samples of the reaction mixture were withdrawn, worked up³ at 1-minute intervals, and analyzed by GC/MS. Under these conditions, only 14 mole % of the *m*-toluic acid⁴ starting material remained after 1 minute of stirring and no starting material was detected after 9 minutes (see figure). The reaction mixture did not turn dark and there was no evidence of the anhydride by-product.



In contrast, identical reaction conditions but in the absence of catalyst still showed 85 mole % *m*-toluic acid after 15 minutes. The remainder of the synthesis was completed using classical Schotten-Baumann conditions. GC/MS analysis of the DEET showed one peak with no evidence of the anhydride. The DEET so obtained was a pale oil (97 % yield) of high purity. A GC/MS comparison of our DEET sample to a commercial sample gave identical chromatograms.

Conclusion

An anhydride by-product and the dark coloration in the DEET product were both eliminated by preparing the toluoyl chloride intermediate (i) without heating, (ii) using 2 drops of pyridine as a catalyst, and (iii) stirring for a short time. The resulting DEET product was a pale oil needing no further purification.

Experimental Details

m-Toluic acid (0.50 g, 3.7 mmol), dry ether (0.20 mL), pyridine (2 drops), and 99.5% SOCl₂ (0.55 mL, 7.6 mmol) were stirred for 8 minutes at room temperature in a loosely stoppered 5-mL round-bottom flask. The reaction was kept in a fume hood; alternatively, the HCl gas liberated may be directed into a short-stemmed funnel connected to an aspirator. The excess SOCl₂ was removed at room temperature under water-aspirator vacuum (25 mm Hg). The reaction solution was pipetted into a mixture of diethylamine (1.3 mL, 12 mmol) in 10% NaOH (5 mL) at 0 °C. After stirring for 1 minute, the solution was extracted twice with 15-mL portions of ether. The ether fractions were dried over MgSO₄ and filtered, and 1 mL of toluene added to azeotropically remove any traces of both water and pyridine. Evaporation of the solvents gave 0.68 g (97%) of DEET as a clear pale oil that gave one peak by GC/MS analysis.

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Notes

1. A later time-consuming vacuum distillation gave a light-colored oil but it was still contaminated with the by-product.

2. HP 5995 GC/MS, 150 °C isothermal run, 5% Ph Me siloxane, 30 m \times 0.25 mm \times 0.25 μ m.

3. The 20- μ L samples were evaporated under vacuum (25 mm Hg) to remove unreacted SOCl₂. The samples were then dissolved in 1 mL of ether and kept on ice for immediate GC/MS analysis. Separate experiments had shown that SOCl₂ rapidly evaporates under these conditions, whereas the acid chloride does not.

4. (Moles *m*-toluic acid/moles *m*-toluoyl chloride) \times 100.

Literature Cited

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2. Sandler, S. R.; Karo, W. *Sourcebook of Advanced Organic Laboratory Preparations*, Academic: San Diego, CA, 1992; p 265.